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REVIEW ARTICLE

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Effectiveness of pre-surgical infant orthopedic treatment for cleft lip and palate patients: a systematic review and meta-analysis

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Abstract

The objective of the study was to systematically summarize current evidence on the effectiveness of pre-surgical infant orthopedics (PSIO) in cleft lip and palate (CLP) patients. Electronic and manual searches were conducted, and using specific inclusion and exclusion criteria, data extraction and analysis was performed by two independent investigators. When possible, overall pooled estimates with 95% confidence intervals were obtained using the random-effects model. Twenty-four of 885 original studies met the inclusion criteria and were included in the qualitative synthesis, whereas 10 of them were included in the quantitative synthesis (meta-analysis). Except for the variable M-T-C(5) assessing maxillary arch form, which presented an increase at 48 months of follow-up, all other variables concerning craniofacial and dentoalveolar changes demonstrated no significant differences, indicating that PSIO treatment has no effect on CLP patients. The limited evidence derived from this study does not seem to support the short- or long-term effectiveness of PSIO in CLP patients.

Key words: cleft lip; cleft palate; meta-analysis; pre-surgical orthopedics; systematic review

Introduction

Clefts of the lip and/or palate (CLP) constitute one of the most frequent craniofacial anomalies. According to the World Health Organization (WHO), one infant in every 600 is born worldwide presenting this defect, which has considerable medical, economic, social, and emotional consequences for the affected individuals and their families (1). The etiology of CLP is complex, involving polygenic interactions with environmental factors. CLP

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patients hence require surgical, orthodontic, dental, nutritional, speech, and psychological scientific support (1). Pre-surgical infant orthopedics (PSIO) refers to the type of treatment that, during infancy and prior to CLP surgical reconstruction, approximates the soft and osseous structures surrounding the cleft (2).

Sixty years after it was introduced by McNeil (3) and later developed by Burston (4), a substantial body of literature has demonstrated various types of orthopedic appliances, such as active ones with screws and pins for retention (5–9) and passive ones with (3, 4) or without (10) extraoral strapping, or with additional nasal stents (11, 12). Despite the numerous applications, the clinical effectiveness of PSIO treatment remains a controversial issue.

Proponents of this approach claim that PSIO treatment guides palatal growth (8, 13–15), improves the esthetic outcome of the nasolabial structures (8, 12, 15–17), and reduces the need for secondary surgeries during the patient's lifetime (12, 13). In addition, they claim that infants' feeding ability (14) and speech development (18–20) and parents' psychology are enhanced (14, 21). In contrast, several authors consider that there is no evidence of esthetic improvement or reduction in the extent of surgical/orthodontic treatment required, and consequently do not agree with these advantages (2, 22–25). Eventually, the fact that PSIO treatment facilitates surgery seems to be the only area of agreement (2, 3, 8, 9, 12, 13, 23, 26–28).

A number of key-points regarding PSIO treatment of CLP patients seem to be overlooked. The majority of the aforementioned two categories of studies lack 1) appropriate study design; 2) statistically adequate sample size; 3) proper description of the patients' characteristics; 4) untreated control group or treated control group with no PSIO; 5) clear outcome measures; and 6) follow-up into adulthood. Consequently, the known beneficial or harmful effects of PSIO treatment are based mainly on studies with low level of evidence (29), a fact that leads to contradictions among scientists and thus to confusion in clinical decision-making.

Therefore, the aim of this investigation was to qualitatively and quantitatively assess the currently existing literature by conducting a systematic review and a meta-analysis of randomized controlled clinical trials (RCTs) and prospective controlled clinical trials (pCCTs) in an attempt to provide the best evidence available on the effectiveness of PSIO treatment in CLP patients and more specifically on general developmental measures, as well as on craniofacial and dentoalveolar treatment outcomes in the short and long term.

Material and methods

This meta-analysis was conducted following a pre-defined protocol including a search strategy, eligibility criteria for study inclusion, screening methods, quality control, data extraction, and data analysis (30), which was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (31).

Data sources and searches

A computerized literature search of several electronic databases was independently conducted by two authors (ENK and MLV) for the identification of eligible studies published up to July 2010, using key words and their combinations, modified according to the syntax rules of each database. Table 1 presents the databases searched and outlines the strategy followed along with the number of studies found in each database. In an attempt to avoid publication bias, gray literature (i.e., articles that have not been formally published) was also searched directly through databases/registers [Google Scholar, UMI Proquest (dissertations and theses), Cambridge Scientific Abstracts (conference proceedings)], ongoing trials (metaRegister of Controlled Trials), and the German National Library of Medicine (technical reports, proceedings, reprints). In addition, publication status was not used as an exclusion criterion. Both English and non-English articles referring to human studies were included. The most recent electronic search was undertaken on September 1, 2010, when the database of the clinical trials (CTs) registers (metaRegister of

Table 1. **The electronic databases searched, the search strategies used, and the corresponding results**

Electronic database	Search strategy used	Extent of search	Hits
MEDLINE searched via PubMed (1950–13 July 2010) http://www.ncbi.nlm.nih.gov/sites/entrez/	((randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh]) OR ('clinical trial' [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study OR evaluation studies OR follow-up studies [mh] OR prospective studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw])) AND ((cleft lip) OR (cleft lip and palate) OR (alveolar cleft*)) AND ((infant orthodontics) OR (infant orthopaedics) OR (infant orthopedics) OR (preoperative orthodontics) OR (preoperative orthopaedics) OR (preoperative orthopedics) OR (presurgical orthodontics) OR (presurgical orthopaedics) OR (presurgical orthopedics) OR (presurgical orthodontic treatment) OR (presurgical orthopaedic treatment) OR (presurgical orthopedic treatment) OR (alveolar molding) OR (alveolar moulding) OR (nasoalveolar molding) OR (nasoalveolar moulding) OR (nasal alveolar molding) OR (nasal alveolar moulding) OR (pnam))	In all fields	237
EMBASE searched via ScienceDirect (1974–13 July 2010) http://www.embase.com	((cleft lip) OR (cleft lip and palate) OR (alveolar cleft*)) AND ((infant orthodontics) OR (infant orthopaedics) OR (infant orthopedics) OR (preoperative orthodontics) OR (preoperative orthopaedics) OR (preoperative orthopedics) OR (presurgical orthodontics) OR (presurgical orthopaedics) OR (presurgical orthopedics) OR (presurgical orthodontic treatment) OR (presurgical orthopaedic treatment) OR (presurgical orthopedic treatment) OR (alveolar molding) OR (alveolar moulding) OR (nasoalveolar molding) OR (nasoalveolar moulding) OR (nasal alveolar molding) OR (nasal alveolar moulding) OR (pnam))	Limited to humans/ in all fields	88
Cochrane Database of Systematic Reviews searched via The Cochrane Library on 13 July 2010 http://www.thecochrane-library.com	((cleft lip) OR (cleft lip and palate) OR (alveolar cleft*)) AND ((infant orthodontics) OR (infant orthopaedics) OR (infant orthopedics) OR (preoperative orthodontics) OR (preoperative orthopaedics) OR (preoperative orthopedics) OR (presurgical orthodontics) OR (presurgical orthopaedics) OR (presurgical orthopedics) OR (presurgical orthodontic treatment) OR (presurgical orthopaedic treatment) OR (presurgical orthopedic treatment) OR (alveolar molding) OR (alveolar moulding) OR (nasoalveolar molding) OR (nasoalveolar moulding) OR (nasal alveolar molding) OR (nasal alveolar moulding) OR (pnam))	In all fields	2
Cochrane Central Register of Controlled Trials searched via The Cochrane Library on 13 July 2010 http://www.thecochrane-library.com	((cleft lip) OR (cleft lip and palate) OR (alveolar cleft*)) AND ((infant orthodontics) OR (infant orthopaedics) OR (infant orthopedics) OR (preoperative orthodontics) OR (preoperative orthopaedics) OR (preoperative orthopedics) OR (presurgical orthodontics) OR (presurgical orthopaedics) OR (presurgical orthopedics) OR (presurgical orthodontic treatment) OR (presurgical orthopaedic treatment) OR (presurgical orthopedic treatment) OR (alveolar molding) OR (alveolar moulding) OR (nasoalveolar molding) OR (nasoalveolar moulding) OR (nasal alveolar molding) OR (nasal alveolar moulding) OR (pnam))	In all fields	31

Table 1. **Continued**

Electronic database	Search strategy used	Extent of search	Hits
Google Scholar Beta searched on 29 July 2010 http://www.scholar.google.com	infant orthodontics		0
	infant orthopaedics		7
	infant orthopedics		18
	preoperative orthodontics		1
	preoperative orthopaedics		1
	preoperative orthopedics		3
	presurgical orthodontics		5
	presurgical orthopaedics		1
	presurgical orthopedics		13
	presurgical orthodontic treatment		10
	presurgical orthopaedic treatment		3
	presurgical orthopedic treatment		10
	alveolar molding		11
	alveolar moulding		0
	nasoalveolar molding		35
	nasoalveolar moulding		3
	nasal alveolar molding		2
	nasal alveolar moulding		0
	pnam		12
Web of Science searched on 15 July 2010 http://scientific.thomson.com/products/wos/	TS=(((randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh]) OR ('clinical trial' [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study OR evaluation studies OR follow-up studies [mh] OR prospective studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw])) AND ((cleft lip) OR (cleft lip and palate) OR (alveolar cleft*)) AND ((infant orthodontics) OR (infant orthopaedics) OR (infant orthopedics) OR (preoperative orthodontics) OR (preoperative orthopaedics) OR (preoperative orthopedics) OR (presurgical orthodontics) OR (presurgical orthopaedics) OR (presurgical orthopedics) OR (presurgical orthodontic treatment) OR (presurgical orthopaedic treatment) OR (presurgical orthopedic treatment) OR (alveolar molding) OR (alveolar moulding) OR (nasoalveolar molding) OR (nasoalveolar moulding) OR (nasal alveolar molding) OR (nasal alveolar moulding) OR (pnam)))	In topic	39
Evidence-Based Medicine searched on 13 July 2010 http://ebm.bmjjournals.com	'cleft lip' OR 'cleft lip and palate'	In all fields	1

Table 1. **Continued**

Electronic database	Search strategy used	Extent of search	Hits
Scopus searched on 13 July 2010 http://www.scopus.com	('cleft lip' OR 'cleft lip and palate' OR 'alveolar cleft*') AND ('infant orthodontics' OR 'infant orthopaedics' OR 'infant orthopedics' OR ' preoperative orthodontics' OR 'preoperative orthopaedics' OR 'preoperative orthopedics' OR 'presurgical orthodontics' OR 'presurgical orthopaedics' OR 'presurgical orthopedics' OR 'presurgical orthodontic treatment' OR 'presurgical orthopaedic treatment' OR 'presurgical orthopedic treatment' OR 'alveolar molding' OR 'alveolar moulding' OR 'nasoalveolar molding' OR 'nasoalveolar moulding' OR 'nasal alveolar molding' OR 'nasal alveolar moulding' OR 'pnam')	In all fields	466
LILACS database searched on 13 July 2010 http://bases.bvs.br	((cleft and lip) or (cleft and lip and palate) or (alveolar and cleft)) and ((infant and orthodontics) or (infant and orthopaedics) or (infant and orthopedics) or (preoperative and orthodontics) or (preoperative and orthopaedics) or (preoperative and orthopedics) or (presurgical and orthodontics) or (presurgical and orthopaedics) or (presurgical and orthopedics) or (presurgical and orthodontic and treatment) or (presurgical and orthopaedic and treatment) or (presurgical and orthopedic and treatment) or (alveolar and molding) or (alveolar and moulding) or (nasoalveolar and molding) or (nasoalveolar and moulding) or (nasal and alveolar and molding) or (nasal and alveolar and moulding) or (pnam))	Limited to humans/ in all fields	14
Bibliografia Brasileira de Odontologia searched on 13 July 2010 http://bases.bvs.br	(((((cleft and lip)) or ((cleft and lip and palate)) or ((alveolar and cleft)))) and ((((infant and orthodontics)) or ((infant and orthopaedics)) or ((infant and orthopedics)) or ((preoperative and orthodontics)) or ((preoperative and orthopaedics)) or ((preoperative and orthopedics)) or ((presurgical and orthodontics)) or ((presurgical and orthopaedics)) or ((presurgical and orthopedics)) or ((presurgical and orthodontic and treatment)) or ((presurgical and orthopaedic and treatment)) or ((presurgical and orthopedic and treatment)) or ((alveolar and molding)) or ((alveolar and moulding)) or ((nasoalveolar and molding)) or ((nasoalveolar and moulding)) or ((nasal and alveolar and molding)) or ((nasal and alveolar and moulding)) or ((pnam))))	In all fields	4
Ovid database searched via Heal-link on 13 July 2010 http://ovidsp.ovid.com/autologin.html	((cleft lip) OR (cleft lip and palate) OR (alveolar cleft*)) AND ((infant orthodontics) OR (infant orthopaedics) OR (infant orthopedics) OR (preoperative orthodontics) OR (preoperative orthopaedics) OR (preoperative orthopedics) OR (presurgical orthodontics) OR (presurgical orthopaedics) OR (presurgical orthopedics) OR (presurgical orthodontic treatment) OR (presurgical orthopaedic treatment) OR (presurgical orthopedic treatment) OR (alveolar molding) OR (alveolar moulding) OR (nasoalveolar molding) OR (nasoalveolar moulding) OR (nasal alveolar molding) OR (nasal alveolar moulding) OR (pnam))	In all fields	302
Bandolier searched on 13 July 2010 http://www.jr2.ox.ac.uk/Bandolier	('cleft lip', 'cleft lip and palate', 'alveolar cleft*')	In all fields	1

Table 1. **Continued**

Electronic database	Search strategy used	Extent of search	Hits
Atypon Link searched on 13 July 2010 http://www.atypon-link.com/	((cleft lip) OR (cleft lip and palate) OR (alveolar cleft*)) AND ((infant orthodontics) OR (infant orthopaedics) OR (infant orthopedics) OR (preoperative orthodontics) OR (preoperative orthopaedics) OR (preoperative orthopedics) OR (presurgical orthodontics) OR (presurgical orthopaedics) OR (presurgical orthopedics) OR (presurgical orthodontic treatment) OR (presurgical orthopaedic treatment) OR (presurgical orthopedic treatment) OR (alveolar molding) OR (alveolar moulding) OR (nasoalveolar molding) OR (nasoalveolar moulding) OR (nasal alveolar molding) OR (nasal alveolar moulding) OR (pnam))	In all fields	7
African Journals Online searched on 13 July 2010 http://www.ajol.info	'cleft lip' OR 'cleft lip and palate' OR 'alveolar cleft*'	In all fields*	21
Digital Dissertations searched via UMI ProQuest on 13 July 2010 http://proquest.umi.com/pqdweb?RQT = 302&cfc = 1	('cleft lip' OR 'cleft lip and palate' OR 'alveolar cleft*') AND ('infant ortho*' OR 'preoperative ortho*' OR 'presurgical ortho*' OR 'alveolar molding' OR 'alveolar moulding' OR 'nasoalveolar molding' OR 'nasoalveolar moulding' OR 'nasal alveolar molding' OR 'nasal alveolar moulding' OR 'pnam')	In all fields (Databases: Dissertations & Theses)	1
Conference Paper Index searched via Cambridge Scientific Abstracts (1982–13 July 2010) http://journals.cambridge.org/action/search	((cleft lip) or (cleft lip and palate) or (alveolar cleft*)) and ((infant orthodontics) or (infant orthopaedics) or (infant orthopedics) or (preoperative orthodontics) or (preoperative orthopaedics) or (preoperative orthopedics) or (presurgical orthodontics) or (presurgical orthopaedics) or (presurgical orthopedics) or (presurgical orthodontic treatment) or (presurgical orthopaedic treatment) or (presurgical orthopedic treatment) or (alveolar molding) or (alveolar moulding) or (nasoalveolar molding) or (nasoalveolar moulding) or (nasal alveolar molding) or (nasal alveolar moulding) or (pnam))	In all fields	2
metaRegister of Controlled Trials (all registers active and archived) searched on 1 September 2010 http://www.controlled-trials.com/mrct/	(cleft lip) OR (cleft lip and palate) OR (alveolar cleft*)	In all fields*	24
German National Library of Medicine (ZB MED) searched on 13 July 2010 http://www.medpilot.de	'cleft lip'	Basic search (Document type: Thesis)	24
Sum			1399

*Limited search capabilities.

Controlled Trials) was searched to identify potentially relevant unpublished or ongoing studies. The reference lists of all relevant review articles were manually searched for studies that had not been possibly identified by the electronic search. For potentially relevant studies in which only the abstract was available, an attempt was made to contact the authors for further details

(their response is mentioned below). In addition when the full texts provided insufficient evidence, the principle investigators of the relevant CTs were contacted to request trial and outcome information, if available. One investigator did reply to such a request (Dr AG Masarei).

Eligibility criteria and study selection

Eligibility was pre-determined with regard to participants, intervention characteristics, comparisons, outcome measures, and study design (PICOS) (31), and verified by comprehensive reading of the reports identified by the search. Initially, the titles and abstracts of all identified studies were screened. For studies with insufficient data in the title and/or abstract, as well as for those deemed to meet the inclusion criteria, the full texts of the articles were obtained to make a clear decision. When the abstract or the full texts were not available, the corresponding authors were contacted by e-mail to provide a copy of their paper. All full-text articles were assessed independently and in duplicate by two authors (ENK and MLV) according to pre-specified inclusion and exclusion criteria (Table 2). Duplicate records such as published articles presented also in conferences, studies with multiple publications, as well as dissertations published also in journals, were excluded. Disagreements were resolved by consulting the first author (MAP) until final consensus was achieved. The level of inter-reviewer agreement regarding the inclusion of potential studies was calculated by Cohen's κ.

Data extraction

Two authors (ENK and MLV) extracted independently all relevant data in the specially pre-designed extraction form after appropriate adjustment. Afterward, the same two authors double-extracted data for a random sample of 10% of the included studies to assess data reliability. Again, any disagreement during the extraction process was resolved by consulting the first author (MAP) until a final consensus was achieved. Inter-reviewer agreement on data extraction was assessed by Cohen's κ.

For each trial, the following data were recorded: 1) author, year of publication, study design, and identification source of each trial; 2) demographic characteristics of the participants; 3) details of the diagnosis, the outcome investigated, and the method by which the latter was assessed; 4) intervention characteristics, such as the type of the appliance used, the time of treatment initiation, and the follow-ups of each trial; and 5) information regarding the authors' conclusions.

Quality analysis

Quality analysis for all included studies was performed independently by two authors (ENK and MLV), as described by Antczack et al. (32) and Jadad et al. (33). These procedures were conducted without blinding, because scientific evidence does not strongly suggest masked assessment (34). Studies were classified as of low (0–5 points), medium (6–8 points), or high (9 or 10 points) quality. Inter-reviewer agreement on quality analysis was assessed by Cohen's κ.

Data synthesis and analysis

For the deduplication of the initially identified records, a reference management tool was used (RefWorks, 2010 ProQuest LLC) and the resulting records were processed using the Microsoft Office Excel software (Microsoft Co., Redmond, WA, USA).

Statistical analysis was performed initially using the statistical software 'SPSS' version 18.0 (SPSS Inc., Chicago, IL, USA). Meta-analysis was undertaken only in cases where there was more than one study reporting the same outcome measures, and was conducted with the specially designed software 'Comprehensive Meta-Analysis' (Biostat Inc, Englewood, NJ, USA) using the random-effects (RE) model (35).

The mean difference (MD) or the standardized mean difference (SMD) was used as the metric of choice for the continuous variables. Because no trials with comparisons across time points were identified, and meta-regression could not be

Table 2. **Eligibility criteria used in this meta-analysis**

Criteria category	Inclusion criteria	Exclusion criteria
Outcome	Studies investigating the effectiveness of pre-surgical orthopedic treatment in patients with complete UCLP during infancy	Investigations not relevant to the subject of this study
Study design	Randomized controlled clinical trials	Prospective uncontrolled clinical trials
	Prospective controlled clinical trials	Retrospective clinical trials
		Unsupported opinion of expert
		Editor's choices
		Books' abstracts
		Conferences' abstracts
		Cross-sectional surveys
		Narrative reviews
		Systematic reviews
		Meta-analyses
		Animal studies
		Replies to the author/editor
		Studies on molecular biology, histology, or genetics
		In vitro studies
		Case series without a control
		Case reports
		Case–control observational studies
		Studies with missing English abstract and/or having no abstract at all
		Ongoing studies
Participants' characteristics	Studies included referring to human studies on infant patients younger than 1 year old at treatment start	Studies evaluating patients with incomplete UCLP or isolated cleft palate
		Human studies referring to infant patients older than 1 year old at treatment start
		Clinical trials with inadequate sample size groups

UCLP, unilateral cleft lip and palate.

employed, results across corresponding trials were pooled, treating each trial arm at a specific time point as an independent cohort. Results were stratified as short-term and long-term effectiveness. p-Values were two-tailed with $\alpha = 0.05$, and all presented confidence intervals (CI) were calculated at the 95% level.

Assessment of publication bias

If three or more compatible studies examining the same outcome were available, our intention was to evaluate publication bias through visual inspection of funnel plot asymmetry (36), which, however, should be seen as a means of examining 'small study effects' and not as tool to diagnose specific types of bias (37).

Heterogeneity assessment

Heterogeneity among trials was assessed using a chi-square test for heterogeneity, significant at $p < 0.10$ (38), and the I^2 measure of inconsistency. I^2 is independent of the number of studies and quantifies heterogeneity on a scale of 0–100%. Heterogeneity was defined as low (25%), moderate (50%), or high (75%) (39–41). The extent of heterogeneity between subgroups of

time points (indicating short- vs. long-term effects) was assessed using the I^2 statistic.

Results

Literature search

The electronic search strategy yielded initially 1449 records. After removing the duplicates, 885 potential studies remained, while no additional records were identified through hand-searching. A total of 770 records did not fulfill the eligibility criteria and were excluded on the basis of their titles and abstracts. The full texts of 22 records were not available and consequently were also excluded because of the following reasons (Table S1): 1) in 10 articles, the contact details of the corresponding authors were not available, and thus, they could not be contacted (Deng et al., 2005; Huddart, 1979; Kato et al., 1999; Li-qin et al., 2007; Mao et al., 2006; Morita et al., 2004; Pollastri et al., 2000; Van der Beek et al., 1992; Xu et al., 2003; Zschiesche, 1991); 2) in 10 articles, the corresponding authors were contacted via e-mail but they did not reply (Deng et al., 2005; Zeng et al., 2005; Fang et al., 1999; Gong et al., 2009; Hamamoto, 1988; Hamamoto et al., 1984; Li et al., 2006; Li et al., 2009; Mølsted et al., 1993; Suzuki et al., 2005); 3) in one article, delivery of e-mail failed owing to technical reasons (Brättstrom, 1991); and 4) in one article, the author did not possess a copy of the publication (Opitz, 1991).

Careful evaluation of the full text of the remaining 93 articles led to the exclusion of 69 trials; 54 were retrospective CTs, 14 were prospective uncontrolled CTs, and one was prospective CT with inadequate sample size (Table S2). Consequently, although a total of 24 trials were included in this review, meta-analysis was possible to be performed for only 10 of them. The number of excluded studies along with the respective reasons for exclusion is presented in Table 3, while the flow diagram of the whole selection procedure is presented in Fig. 1.

The κ score for the selection of studies was 0.837, indicating an almost perfect level of inter-reviewer agreement (42).

Table 3. **Number of the excluded articles in this meta-analysis according to the exclusion criteria**

Exclusion criteria	Number of excluded articles
Investigations not relevant to the subject of this study	573
Prospective uncontrolled clinical trials	14
Prospective clinical trials with inadequate sample size groups	1
Retrospective clinical trials	54
Unsupported opinion of expert	17
Editor's choices	0
Books' abstracts	6
Conferences' abstracts	26
Cross-sectional surveys	2
Reviews	19
Systematic reviews	0
Meta-analysis	1
Animal studies	5
Replies to the author/editor	12
Studies on molecular biology, histology, or genetics	1
In vitro studies	0
Case series without a control	22
Case reports or reports of cases	40
Case–control observational studies	0
Studies with missing English abstract and/or having no abstract at all	42
Ongoing studies	2
Human studies that refer to infant patients older than 1 year old at treatment start	2
Full text unavailable	22
Total	861

Study characteristics

Of the 24 included trials, 18 were RCTs (43–60) and six were prospective controlled clinical trials (pCCTs) (61–66). Their characteristics are described in Table 4. The κ score for the data extraction indicated an almost perfect level of inter-reviewer agreement. Seventeen RCTs (43–53, 55–60) were reports of the same project (Dutchcleft), evaluating, however, different treatment outcomes at different ages. All trials

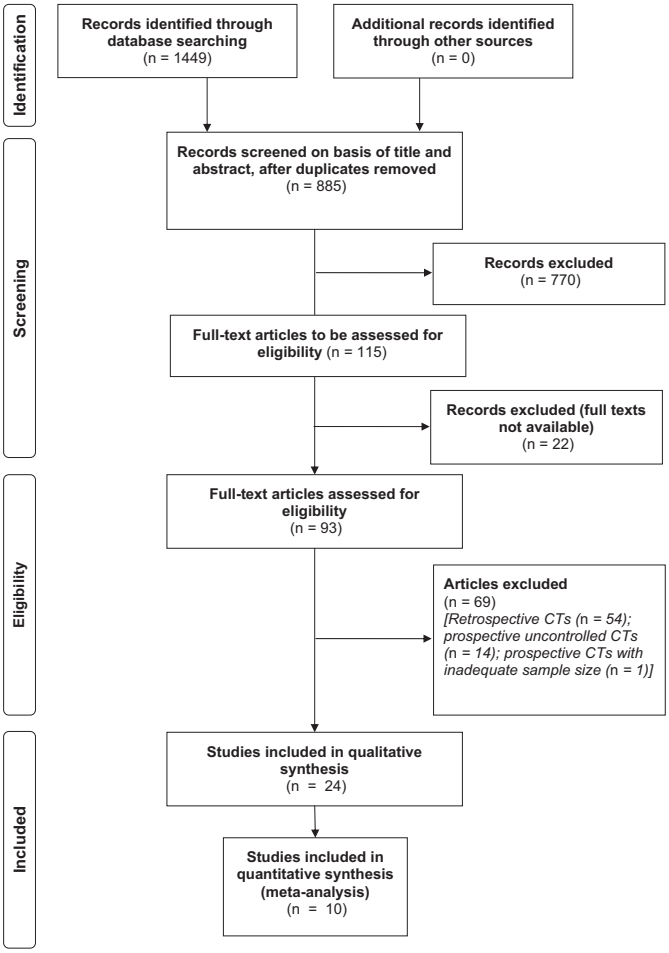

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of the retrieved studies through the selection process.

examined infants with unilateral cleft lip and palate (UCLP), except one (66), which examined infants with bilateral cleft lip and palate (BCLP). The majority of the included trials used a consecutive series of infants (61–65), except for the Dutchcleft studies (43–53, 55–60), and the one of Masarei et al. (54), which conducted a computerized allocation method based on birth weight and alveolar cleft width and on parity and gender, respectively. Apart from the randomization, there were many differences among the surgical protocols used in each trial, such as different surgical techniques and different times of lip and palatal surgery, fluctuating between 3–5 and 6–18 months, respectively. In the majority of the trials, a passive PSIO appliance was used, with the exception of the study by Masarei et al. (54) in which an active appliance was used in infants with complete CLP and a passive one in infants with isolated cleft palate (CP).

Control groups in all included trials consisted of infants with CLP that did not receive any type of PSIO (passive or active). In addition, Mishima et al. (65) examined at the same time also untreated groups of infants with incomplete UCLP, while Masarei et al. (54) infants with isolated CP. However, these types of clefts were not evaluated in the current investigation.

Craniofacial and dentoalveolar treatment changes were measured by cephalometric or study model analysis, respectively, while changes in facial appearance were measured using the Visual Analog Scale (VAS) method. Feeding was evaluated using various tools: Neonatal Oral Motor Assessment Scale (NOMAS), Great Ormond Street Measurement of Infant Feeding (GOSMIF), Schedule for Oral-Motor Assessment (SOMA),

Table 4. **Characteristics of the studies included in the meta-analysis**

No.	Study*	Source	Study design	Sample origin	Initial sample size (M/F)	Diagnosis	Outcome investigated	Measurement method	PSIO appliance	Treatment initiation after birth	Treatment follow-ups after birth	Reported effects
1	Bongaarts et al. (43)	Electronic searching (PubMed, Google Scholar, CENTRAL)	RCT	Caucasian infants from three academic CP centers in the Netherlands (Nijmegen, Amsterdam, and Rotterdam) fluent in the Dutch language	54 (41/13)	Complete UCLP	Occlusion	Plaster casts, 5-year-old index	Zurich type† (passive appliance without external strapping)	Within 2 weeks	At 192 and 288 weeks	No significant differences found between the two groups regarding occlusion of the deciduous dentition
2	Bongaarts et al. (45)	Electronic searching (PubMed, CENTRAL)	RCT	Caucasian infants from three academic CP centers in the Netherlands (Nijmegen, Amsterdam, and Rotterdam) fluent in the Dutch language	54 (41/13)	Complete UCLP	Facial growth	Cephalometric analysis	Zurich type (passive appliance without external strapping)	Within 2 weeks	At 192 and 288 weeks	At 4 years of age, the interincisal angle in the treated group was about 9° larger, but faded away at 6 years of age, and at 6 years, the mentolabial angle was almost 9° smaller. On the whole, cephalometric outcomes provide no clinically identified effect of PSIO on facial growth
3	Bongaarts et al. (46)	Electronic searching (PubMed, CENTRAL)	RCT	Caucasian infants from three academic CP centers in the Netherlands (Nijmegen, Amsterdam, and Rotterdam) fluent in the Dutch language	54 (41/13)	Complete UCLP	Facial appearance	Full-face and nasolabial photographs, professionals and lay observers' judgments, VAS method	Zurich type (passive appliance without external strapping)	Within 2 weeks	At 192 and 288 weeks	PSIO had a positive effect on full-facial appearance at 4 years of age, but until 6 years of age, this was identified only by professionals on the nasolabial photographs. This difference is non-identifiable by the patients
4	Bongaarts et al. (44)	Electronic searching (PubMed, CENTRAL)	RCT	Caucasian infants from three academic CP centers in the Netherlands (Nijmegen, Amsterdam, and Rotterdam) fluent in the Dutch language	54 (41/13)	Complete UCLP	Maxillary arch dimensions	Three-dimensional analysis on plaster casts	Zurich type (passive appliance without external strapping)	Within 2 weeks	At 192 and 288 weeks	All significant differences between the two groups faded away at the age of 6 years. PSIO has no clinically significant effect on the maxillary arch dimension or on the contact and collapse scores

Table 4. **Continued**

No.	Study*	Source	Study design	Sample origin	Initial sample size (M/F)	Diagnosis	Outcome investigated	Measurement method	PSIO appliance	Treatment initiation after birth	Treatment follow-ups after birth	Reported effects
5	Konst et al. (47)	Electronic searching (Embase, Google Scholar, CENTRAL, Web of Science, Scopus)	RCT	Caucasian infants from three academic CP centers in the Netherlands (Nijmegen, Amsterdam, and Rotterdam) fluent in the Dutch language	54 (41/13)	Complete UCLP	Pre-lexical development	Speech recordings, trained listeners' judgments	Zurich type (passive appliance without external strapping)	Within 2 weeks	At 48 and 72 weeks.	At 12 months of age, infants in the treated group showed improved production only of alveolar contoids in contrast with the control group, but at 18 months of age, no significant differences found between the two groups. PSIO had a positive, but only temporary effect on the use of alveolar articulation
6	Konst et al. (49)	Electronic searching (Google Scholar)	RCT	Caucasian infants from three academic CP centers in the Netherlands (Nijmegen, Amsterdam, and Rotterdam) fluent in the Dutch language	54 (41/13)	Complete UCLP	Phonetic characteristics of babbling	Speech recordings, trained listeners' judgments	Zurich type (passive appliance without external strapping)	Within 2 weeks	At 48, 72, and 120 weeks	The better judged speech intelligibility and the lesser compensatory articulation in the 2.5-year-old treated infants were attributed to the higher use of oral plosives and higher occurrence of alveolar contoids in their babbling at 1.5 years of age, respectively. However, it could not be established whether these outcomes were directly related to PSIO
7	Konst et al. (53)	Electronic searching (PubMed, CENTRAL, Web of Science)	RCT	Caucasian infants from three academic CP centers in the Netherlands (Nijmegen, Amsterdam, and Rotterdam) fluent in the Dutch language	54 (41/13)	Complete UCLP	Cost-effectiveness of PSIO regarding speech	Euro (€) per point speech quality improvement	Zurich type (passive appliance without external strapping)	Within 2 weeks	At 120 weeks	Significantly higher cost and higher ratings of speech quality obtained for the treated group. The cost-effectiveness for the treated group was $1041 for 1.34 point speech quality improvement. Thus, from the perspective of speech development, the cost-effectiveness of the treatment with PSIO over the one without PSIO seems acceptable

Table 4. **Continued**

No.	Study*	Source	Study design	Sample origin	Initial sample size (M/F)	Diagnosis	Outcome investigated	Measurement method	PSIO appliance	Treatment initiation after birth	Treatment follow-ups after birth	Reported effects
8	Konst et al. (51)	Electronic searching (PubMed, Google Scholar, CENTRAL, Web of Science)	RCT	Caucasian infants from three academic CP centers in the Netherlands (Nijmegen, Amsterdam, and Rotterdam) fluent in the Dutch language	54 (41/13)	Complete UCLP	Language skills	Speech recordings, Reynell test, and standardized Dutch language tests	Zurich type (passive appliance without external strapping)	Within 2 weeks	At 96, 120, 144, and 288 weeks	PSIO had no significant effect on the receptive language skills at either age. The expressive language skills were influenced, with longer utterances produced by the treated infants at 2.5 and 3 years of age, but these positive outcomes were vanished at 6 years of age. PSIO had no long-term effects on language development
9	Konst et al. (50)	Electronic searching (PubMed, Google Scholar, CENTRAL, Web of Science, Scopus)	RCT	Caucasian infants from three academic CP centers in the Netherlands (Nijmegen, Amsterdam, and Rotterdam) fluent in the Dutch language	54 (41/13)	Complete UCLP	Phonological development	Speech recordings, FAN assessment by phonologists	Zurich type (passive appliance without external strapping)	Within 2 weeks	At 96, 120, and 144 weeks	In the treated group, infants followed a more normal path of phonological development between 2 and 3 years of age, had acquired higher initial consonants at the age of 3 years and a longitudinal analysis revealed significantly less nasal escape at 3 years of age, which was not present in the respective separate analysis. PSIO thus affected the phonological development of the children in this trial; however, it can be expected that both groups will catch up
10	Konst et al. (52)	Electronic searching (PubMed, CENTRAL, Web of Science, Scopus)	RCT	Caucasian infants from three academic CP centers in the Netherlands (Nijmegen, Amsterdam, and Rotterdam) fluent in the Dutch language	54 (41/13)	Complete UCLP	Speech characteristics	Speech recordings, trained listeners' judgments, EAI scale (13 characteristics)	Zurich type (passive appliance without external strapping)	Within 2 weeks	At 120 weeks	Significantly higher ratings obtained in the treated group, but only for intelligibility. Intelligibility of the treated 2.5-year-old-infants was superior and this positive effect of PSIO may be considered as clinically relevant, because the effect size was found to be large

Table 4. **Continued**

No.	Study*	Source	Study design	Sample origin	Initial sample size (M/F)	Diagnosis	Outcome investigated	Measurement method	PSIO appliance	Treatment initiation after birth	Treatment follow-ups after birth	Reported effects
11	Konst et al. (48)	Electronic searching (PubMed, CENTRAL, Scopus)	RCT	Caucasian infants from three academic CP centers in the Netherlands (Nijmegen, Amsterdam, and Rotterdam) fluent in the Dutch language	54 (41/13)	Complete UCLP	Speech intelligibility	Speech recordings, lay listeners' assessments	Zurich type (passive appliance without external strapping)	Within 2 weeks	At 120 weeks	Infants in the treated group were rated with higher intelligibility; however, data obtained by means of transcriptions showed no group differences. PSIO may enhance the desirability of the perceived speech, but improved speech intelligibility should not be expected as a result of the pre-surgical orthopedic treatment
12	Lohmander et al. (61)	Electronic searching (PubMed, Google Scholar, Scopus)	pCCT	Caucasian infants treated by the cleft team at Sahlgrenska University Hospital, Göteborg, Sweden	20 (13/7)	Complete UCLP	Cleft width; Early speech production	Vernier caliper, plaster casts; Speech recordings, listeners' (speech-language pathologists) judgments	Intraoral plate-obturator (passive appliance)	At about 2 weeks of age	At 72 weeks	No significant differences between the two groups regarding the number of consonant tokens or types, neither the manners nor places of articulation, although there was a trend of a significantly higher occurrence of velar plosives in the untreated group. PSIO did not appear to improve the consonant production
13	Masarei et al. (54)	Electronic searching (PubMed, CENTRAL, Scopus, metaRegister of Controlled Trials)	RCT	Infants referred to the North Thames Regional Cleft Centre, Great Ormond Street Hospital for Children NHS Trust, London, UK	34 (21/12‡)	Complete UCLP	Feeding	NOMAS, GOSMIF, video fluoroscopy, anthropometry at 3 months; SOMA, anthropometry at 12 months	Active orthopedic appliance.	Before 2 weeks of age	At 12 and 48 weeks	Infants treated with PSIO were shorter and lighter, with lower body mass index, but none of these outcomes were statistically significant at either age. PSIO did not improve feeding efficiency evaluated by general anthropometric growth data
14	Mishima et al. (64)	Electronic searching (PubMed, Scopus)	pCCT	Infants attended the Second Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Osaka University, Japan, between January 1990 and July 1993	20 (14/6)	Complete UCLP	Palatal forms	Three-dimensional cast analysis	Hotz plate† (passive appliance without external strapping)	At the 2nd or 3rd week after birth	At 16, 24, and 72 weeks	The greater width of the palate and the smaller degree of the palate curvature observed at 18 months of age in the treated group remain up to 4 years of age, indicating that PSIO plays a principal role in growth stimulation and collapse prevention of the maxillary segments. However, no significant differences found between the groups at 4 years of age regarding alveolar arch form and anteroposterior length of the palate

Table 4. **Continued**

No.	Study*	Source	Study design	Sample origin	Initial sample size (M/F)	Diagnosis	Outcome investigated	Measurement method	PSIO appliance	Treatment initiation after birth	Treatment follow-ups after birth	Reported effects
15	Mishima et al. (65)	Electronic searching (PubMed)	pCCT	Infants attended the Second Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Osaka University, Japan, between January 1990 and July 1993	20 (14/6)	Complete UCLP	Palatal forms	Three-dimensional cast analysis	Hotz plate (passive appliance without external strapping)	At the 2nd or 3rd week after birth	At 16, 24, 72, and 192 weeks	In this paper, differences between complete and incomplete cleft lip and palate patients treated with PSIO were examined. No authors' conclusions were drawn regarding the effects on the treated group in comparison with the untreated control group
16	Mishima et al. (62)	Electronic searching (Scopus)	pCCT	Infants attended the Second Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Osaka University, Japan, between January 1990 and July 1993	20 (14/6)	Complete UCLP	Palatal forms	Three-dimensional cast analysis	Hotz plate (passive appliance without external strapping)	At the 2nd or 3rd week after birth	At 16, 24, and 72 weeks	Greater size of the palate, smaller sagittal gap between the maxillary segments, smaller degree of the palate curvature, and greater magnitude of migration of the lesser segment toward the major in the treated group suggest that PSIO could prevent the collapse of the arch from the force of lip closure, stimulate and guide the growth of the maxillary segments, but only during the early period after birth
17	Mishima et al. (63)	Electronic searching (Scopus)	pCCT	Infants attended the Second Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Osaka University, Japan, between January 1990 and July 1993	20 (14/6)	Complete UCLP	Palatal forms	Three-dimensional cast analysis	Hotz plate (passive appliance without external strapping)	At the 2nd or 3rd week after birth	At 16 weeks	At 4 months of age, in the treated group, the degree of the palate curvature was smaller and the maxillary segments moved mesially, whereas in the control group, the segments shifted anteriorly and laterally. PSIO could exclude abnormal force on palatal shelves and normalize intraoral environment

Table 4. **Continued**

No.	Study*	Source	Study design	Sample origin	Initial sample size (M/F)	Diagnosis	Outcome investigated	Measurement method	PSIO appliance	Treatment initiation after birth	Treatment follow-ups after birth	Reported effects
18	Peat (66)	Electronic searching (Google Scholar)	pCCT	Infants treated at Middlemore Hospital, Auckland, New Zealand. They were all assumed to be Caucasians	40	Complete BCLP	Incidence of crossbite; Facial growth	Study models; Cephalometric analysis	Split-palate expansion appliance (passive appliance with external strapping)	At 2 weeks of age	At 240 and 440 weeks	Significantly greater incisor crossbite in the control (untreated) group in both the deciduous and mixed dentition. No significant differences found in the skeletal growth in the anteroposterior direction
19	Prahl et al. (57)	Electronic searching (PubMed, CENTRAL, Web of Science)	RCT	Caucasian infants from three academic CP centers in the Netherlands (Nijmegen, Amsterdam, and Rotterdam) fluent in the Dutch language	54 (41/13)	Complete UCLP	Feeding	Feeding log/ questionnaires, anthropometric data	Zurich type (passive appliance without external strapping)	Within 2 weeks	At 3, 6, 15, and 24 weeks	PSIO had no significant effect on feeding or consequent nutritional status
20	Prahl et al. (56)	Electronic searching (PubMed, CENTRAL, Web of Science)	RCT	Caucasian infants from three academic CP centers in the Netherlands (Nijmegen, Amsterdam, and Rotterdam) fluent in the Dutch language	54 (41/13)	Complete UCLP	Prevention of collapse of alveolar segments	Plaster casts, ordinal scoring system, assessments by orthodontists specialists in CLP	Zurich type (passive appliance without external strapping)	Within 2 weeks	At 15, 24, 48, 58, and 78 weeks of age after birth	No significant differences found between the two groups. PSIO did not facilitate initial contact, neither collapse prevention nor had a positive effect on the severity of collapse from birth until the age of 18 months
21	Prahl et al. (55)	Electronic searching (PubMed, CENTRAL)	RCT	Caucasian infants from three academic CP centers in the Netherlands (Nijmegen, Amsterdam, and Rotterdam) fluent in the Dutch language	54 (41/13)	Complete UCLP	Maxillary arch dimensions	Three-dimensional cast analysis	Zurich type (passive appliance without external strapping)	Within 2 weeks	At 15, 24, 48, and 78 weeks	Alveolar, midpalatal, and posterior cleft width were significantly reduced in the treated group, but these outcomes did not last beyond surgical soft palate closure. PSIO had a significant but temporary effect on maxillary arch dimensions

Table 4. **Continued**

No.	Study*	Source	Study design	Sample origin	Initial sample size (M/F)	Diagnosis	Outcome investigated	Measurement method	PSIO appliance	Treatment initiation after birth	Treatment follow-ups after birth	Reported effects
22	Prahl et al. (58)	Electronic searching (PubMed, CENTRAL)	RCT	Caucasian infants from three academic CP centers in the Netherlands (Nijmegen, Amsterdam, and Rotterdam) fluent in the Dutch language	54 (41/13)	Complete UCLP	Facial appearance	Photographs, professionals and lay observers' judgments, reference scores and VAS method (1–100)	Zurich type (passive appliance without external strapping)	Within 2 weeks	At 72 weeks	No significant differences found between the two groups, regarding early facial appearance. Between the two response modalities used, reference scores appeared to be more discriminative than VAS method
23	Prahl et al. (59)	Electronic searching (PubMed, Google Scholar, CENTRAL)	RCT	Caucasian infants from three academic CP centers in the Netherlands (Nijmegen, Amsterdam, and Rotterdam) fluent in the Dutch language	54 (41/13)	Complete UCLP	Satisfaction in motherhood	Satisfaction questionnaire, 4-point scale	Zurich type (passive appliance without external strapping)	Within 2 weeks	At 6, 24, and 58 weeks	No differences found between the two groups, regarding the effect on mother's satisfaction in motherhood
24	Severens et al. (60)	Electronic searching (PubMed, Google Scholar, CENTRAL, Web of Science)	RCT	Caucasian infants from three academic CP centers in the Netherlands (Nijmegen, Amsterdam, and Rotterdam) fluent in the Dutch language	52	Complete UCLP	Cost-effectiveness of PSIO expressed in duration of surgical lip closure	US Dollars ($) per minute of operating time	Zurich type (passive appliance without external strapping)	Within 2 weeks	At 18 weeks	The mean medical cost for the treated group was significantly higher. The duration of the surgical lip repair did not differ significantly between the two groups

CENTRAL, Cochrane Central Register of Controlled Trials; M/F, male/female; PSIO, pre-surgical infant orthopedics; RCT, randomized controlled trial; pCCT, prospective controlled clinical trial; NR, not reported; UCLP, unilateral cleft lip and palate; BCLP, bilateral cleft lip and palate; VAS, Visual Analog Scale; FAN, Fonologische Analyse van het Nederlands; EAI, equal-appearing interval; NOMAS, Neonatal Oral Motor Assessment; GOSMIF, Great Ormond Street measurement of infant feeding; SOMA, Schedule for Oral-Motor Assessment; CP, cleft palate.

*Authors are in alphabetical order.

†The terms 'Zurich type' and 'Hotz plate' used by the authors refer to the exact same type of appliance.

‡Not reported gender for one infant withdrawn from the trial.

video fluoroscopy, and anthropometry. Speech development was assessed by speech recordings, Reynell test, standardized Dutch language tests, and trained listeners' or language pathologists' judgments.

Quality analysis

Quality evaluation of the trials was performed by taking into account factors that could introduce bias to the results, such as small sample size, different surgical protocols, and different number and experience of surgeons. The overall quality of the included trials averaged 7 out of 10 points, and thus, it was evaluated as 'medium' (Table 5). The highest quality score was given to the Dutchcleft studies (43–53, 55–60), because they were the best-designed. However, even though in many of the studies the existence of confounding factors (most common being operator bias) was taken into consideration by the researchers, it was not possible to eliminate them.

The level of inter-reviewer agreement for each of the eight variables used for the quality analysis of the included studies, evaluated by Cohen's κ, was almost perfect for six variables and substantial for the remaining two (Table 6). The ratings of the two authors (ENK and MLV) with regard to the ranking of the included studies did not differ statistically ($p = 0.249$).

Assessment of publication bias

Publication bias was not possible to assess, because not more than two studies were possible to be included in the meta-analytical comparisons undertaken for each variable under investigation.

Data synthesis and heterogeneity assessment

Our initial intension was to assess the clinical effectiveness of PSIO treatment for CLP patients by evaluating the maximum number of parameters, assessing general developmental measures, as well as craniofacial and dentoalveolar treatment outcomes in the long term. Despite the fact that available data were limited, a total of 13 comparisons were made, concerning a small number of the variables assessed in the original articles evaluating the aforementioned characteristics. These included weight, height, speech, sagittal development of maxilla and mandible, craniofacial growth pattern, as well as maxillary arch depth, width, and form (Table 7, Figs 2–5). Thus, parameters such as facial esthetics, occlusion, collapse and contact status, cost-effectiveness, as well as motherhood satisfaction, were only systematically reviewed.

General developmental measures

PSIO seems to have no effects on weight, height, and feeding, because no significant differences were found for these variables between CLP patients who received PSIO treatment (PSIO+) in comparison with CLP patients who did not receive such treatment (PSIO−).

Weight/height differences between PSIO+ and PSIO− CLP patients were examined in two studies (54, 57), via the 'z-scores' for weight and height. The pooled MD of weight between these two groups was 0.12 kg (95% CI = −0.34 to 0.58; $p = 0.607$) at 3–4 months and 0.04 kg (95% CI = −0.48 to 0.56; $p = 0.885$) at 12 months (Fig. 2A), while the MD of height was −0.06 cm (95% CI = −0.54 to 0.42 cm; $p = 0.820$) and −0.02 cm (95% CI = −0.52 to 0.49 cm; $p = 0.948$) for the corresponding time points (Fig. 2B). Speech development was assessed by means of Fonologische Analyse van het Nederlands (FAN) assessment and International Phonetic Alphabet (IPA) by the two studies (50, 61) included in the analysis, respectively, after a 1.5–2 years of follow-up. Its pooled SMD between PSIO+ and PSIO− patients was 0.12 (95% CI = −1.26 to 1.51; $p = 0.863$) (Fig. 3).

No standardized or non-standardized MD was significant, indicating that PSIO has no significant beneficial effect on weight, height, and speech development of CLP patients at any time. No significant heterogeneity was present between the subgroups of time points for any of the three variables, indicating that the long-term effects of PSIO treatment on weight, height, and speech development did not differ from the short-term effects.

Table 5. **Quality evaluation of the included studies**

No.	Study*	Study design	Sample size	Selection description	Valid measurement methods	Method error analysis	Blinding in measurements	Adequate statistics provided	Confounding factors	Score	Judged quality standard
1	Bongaarts et al. (43)	3	1	1	1	1	1	1	0	9	High
2	Bongaarts et al. (45)	3	1	1	1	1	1	1	0	9	High
3	Bongaarts et al. (46)	3	1	1	1	1	1	1	0	9	High
4	Bongaarts et al. (44)	3	1	1	1	1	1	1	0	9	High
5	Konst et al. (47)	3	1	1	1	1	1	1	0	9	High
6	Konst et al. (53)	3	1	1	1	1	1	1	0	9	High
7	Konst et al. (50)	3	1	1	1	1	1	1	0	9	High
8	Konst et al. (51)	3	1	1	1	1	1	1	0	9	High
9	Konst et al. (52)	3	1	1	1	1	1	1	0	9	High
10	Konst et al. (48)	3	1	1	1	1	1	1	0	9	High
11	Konst et al. (49)	3	1	1	1	1	1	1	0	9	High
12	Lohmander et al. (61)	1	0.5	1	1	1	0	1	0	5.5	Low–Medium
13	Masarei et al. (54)	3	1	1	1	0	1	1	0	8	Medium
14	Mishima et al. (64)	1	0.5	1	1	0	0	1	0	4.5	Low
15	Mishima et al. (65)	1	0.5	1	1	0	0	1	0	4.5	Low
16	Mishima et al. (62)	1	0	1	1	0	0	1	0	4	Low
17	Mishima et al. (63)	1	0	1	1	0	0	1	0	4	Low
18	Peat (66)	1	0	0.5	1	0	0	1	1	4.5	Low
19	Prahl et al. (57)	3	1	1	1	1	1	1	0	9	High
20	Prahl et al. (56)	3	1	1	1	1	1	1	0	9	High
21	Prahl et al. (55)	3	1	1	1	1	1	1	0	9	High
22	Prahl et al. (58)	3	1	1	1	1	1	1	0	9	High
23	Prahl et al. (59)	3	1	1	1	1	1	1	0	9	High
24	Severens et al. (60)	3	1	1	1	1	1	1	0	9	High
Overall estimate										7	Medium

The following eight variables were evaluated: study design (randomized controlled clinical trials = 3 points; prospective study = 1 point; retrospective study = 0 point); sample size (adequate = 1 point; partly inadequate = 0.5 point; inadequate = 0 point); selection description (adequate = 1; partly inadequate = 0.5; inadequate = 0); valid measurement methods = 1 point; use of method error analysis = 1 point; use of blinding in measurements = 1 point; confounding factors estimated in analysis = 1 point. In summary, a study could maximally score 10 points and was categorized of low (0–5 points), medium (6–8), or high (9–10) quality.

*Authors in alphabetical order.

Craniofacial treatment outcomes

The skeletal pattern was examined in two studies (45, 66) via three cephalometric variables: the angles SNA (Fig. 4A), SNB (Fig. 4B) and SN-MP (mandibular plane angle) (Fig. 4C). The pooled MD of the SNA angle between PSIO+ and PSIO− groups of patients was 1.24° (95% CI = −0.81 to 3.29°; $p = 0.246$) at the 4–5 years of follow-up and 1° (95% CI = −2.62 to 4.62°; $p = 0.588$) at the 9.2 years of follow-up. The pooled MD in SNB angle between PSIO+ and PSIO− patients was 1.8° (95% CI = −0.10 to 3.69°; $p = 0.063$) and −2° (95% CI = −5.14 to 1.14°; $p = 0.212$) at the corresponding time points. The pooled MD in SN-MP angle between PSIO+ and PSIO- patients was −0.61° (95% CI = −2.44 to 1.21°; $p = 0.511$) and −1° (95% CI = −4.81 to 2.81°; $p = 0.607$) at the corresponding time points.

No significant MDs were found for all the aforementioned variables (Table 7), indicating that no significant differences exist among PSIO+ and PSIO− patients concerning skeletal pattern. Further, no significant heterogeneity was present between the subgroups of time points for SNA or SN-MP, indicating that the

Table 6. **κ scores measuring level of agreement between the two authors in assessing the quality of the included articles**

Parameters	κ value	Level of agreement
Study design	1.0	Almost perfect
Sample size	0.795	Substantial
Selection description	1.0	Almost perfect
Valid measurement methods	1.0	Almost perfect
Method error analysis	0.895	Almost perfect
Blinding in measurements	1.0	Almost perfect
Adequate statistic provided	1.0	Almost perfect
Confounding factors	0.795	Substantial

Level of agreement. $\kappa < 0.00$: poor; $\kappa = 0.00$–0.20: slight; $\kappa = 0.21$–0.40: fair; $\kappa = 0.41$–0.60: moderate; $\kappa = 0.61$–0.80: substantial; $\kappa = 0.81$–1.00: almost perfect.

long-term effect of PSIO on these variables did not differ from the short-term effect. A non-significant trend toward a higher SNB angle of PSIO+ patients was observed at the 4–5 years of follow-up by a MD of 1.80°; $p = 0.063$; the effectiveness of PSIO in improving the SNB angle diminished significantly (the MD changed from 1.8° to −2°) between 4–5 and 9.2 years (between time points $p = 0.042$). However, for both the SNA and SNB angles, data synthesis was undertaken by comparing data from UCLP and BCLP patients at T1 with data from BCLP patients at T2, and thus, the corresponding results must be viewed with caution.

Dentoalveolar treatment outcomes

The dentoalveolar changes in the maxillary arch were measured by means of special 3D measurement equipment (3D Tristation®; 3D Reflex Microscope®) in two series of studies (43, 55, 62–65) at four time points: at 1–2 weeks (T1), at 6 months (T2), at 18–19.5 months (T3), and at 48 months (T4).

The maxillary arch depth was examined by measuring the depth perpendicular from the top of the interdental papilla between the central incisors (I) to the intertuberosity point distance (TT′). The pooled MD of this variable between PSIO+ and PSIO− patients was 0.16 mm (95% CI = −2.15 to 2.47 mm; $p = 0.895$) at T1, −0.13 mm (95% CI = −2.28 to 2.03 mm; $p = 0.909$) at T2, 0.13 mm (95% CI = −2.31 to 2.57 mm; $p = 0.915$) at T3, and 1.15 mm (95% CI = −1.03 to 3.32 mm; $p = 0.301$) at T4 (Fig. 5A).

The maxillary anterior and posterior arch width was examined by measuring 1) the distance between the maxillary tuberosities (TT′) (Fig. 5B); 2) the distance between the most occlusal point of the cusp of the upper canine [C(5)-(5)′] (Fig. 5C); and 3) the distance between the most occlusal point of the palatal cusp of the upper second deciduous molars or second pre-molars [P2(5)-(5)′] (Fig. 5D).

No significant MDs were found for all the aforementioned variables (Table 7), indicating that no significant differences exist among PSIO+ and PSIO− patients concerning maxillary arch depth or width. Further, no significant heterogeneity was present between the subgroups of time points for any of the depth or width measurements, indicating that the long-term effect of PSIO on maxillary arch depth and maxillary arch width did not differ from the short-term effect. The comparison regarding the distance between the upper canines [C(5)-(5)′] included almost entirely data from one original study, and thus no meta-analytic comparison between the time points was possible to be made (Fig. 5C).

There is a possibility that the form of the maxillary dental arch was slightly affected when CLP patients received PSIO. The maxillary arch form was examined via three angles measured: 1) M-T-C(5), the angle formed between the midpoint of the tuberosity line (M), the tuberosity at the unclefted side (T), and the most occlusal point of the canine cusp at the unclefted side [C(5)] (Fig. 5E); 2) M-T′-C(5)′, the corresponding angle at the cleft side (Fig. 5F); and 3) P′-C(5)-T, the angle contained by the larger segment margin anteriorly at the unclefted side (P′), the most occlusal point of the canine cusp at the unclefted side [C(5)], and the tuberosity at the unclefted side (T) (Fig. 5G).

The angle M-T-C(5) presented small, but significant differences between PSIO+ and PSIO− patients, yet in only two of the four time points assessed, including the post-surgical baseline

Table 7. **Summary of pooled estimates for the meta-analyses**

Variable	Time point	Follow-up	Sample size (*n*) PSIO+/PSIO–	No of studies	Heterogeneity (I^2), %	Metric (RE)	Point estimate	95% Confidence interval	*p*-Value[#]	Between time points *p*-Value (compared to T1)
Weight (kg) (Fig. 2A)	T1	3/4 months	35/37	2	0	MD	0.12	–0.34 to 0.58	0.607	–
	T2	12 months	31/28	2	0		0.04	–0.48 to 0.56	0.885	0.818
Height (cm) (Fig. 2B)	T1	3/4 months	35/37	2	0	MD	–0.06	–0.54 to 0.42	0.820	–
	T2	12 months	31/28	2	0		–0.02	–0.52 to 0.49	0.948	0.913
Speech (Fig. 3)	T1	1.5/2 years	18/16	2	75	SMD	0.12	–1.26 to 1.51	0.863	–
SNA (°) (Fig. 4A)	T1	4/5 years	37/27	2	0	MD	1.24	–0.81 to 3.29	0.246	–
	T2	9.2 years	14/12	1	0		1.00	–2.62 to 4.62	0.588	0.917
SNB (°) (Fig. 4B)	T1	4/5 years	31/24	2	0	MD	1.80	–0.10 to 3.69	0.063	–
	T2	9.2 years	14/12	1	0		–2.00	–5.14 to 1.14	0.212	**0.042***
SN-MP (mm) (Fig. 4C)	T1	4/5 years	31/24	2	0	MD	–0.61	–2.44 to 1.21	0.511	–
	T2	9.2 years	14/12	1	0		–1.00	–4.81 to 2.81	0.607	0.858
Maxillary arch depth	T1	0 months	35/30	2	69	MD	0.16	–2.15 to 2.47	0.895	–
(mm) (Fig. 5A)	T2	6 months	33/29	2	54		–0.13	–2.28 to 2.03	0.909	0.887
	T3	18/19.5 months	26/26	2	0		0.13	–2.31 to 2.57	0.915	0.935
	T4	48 months	33/27	2	88		1.15	–1.03 to 3.32	0.301	0.666
Maxillary arch width 1	T1	0 months	35/30	2	0	MD	–0.42	–3.71 to 2.86	0.800	–
(TT′) (mm) (Fig. 5B)	T2	6 months	33/29	2	30		0.39	–3.04 to 3.81	0.825	0.905
	T3	18/19.5 months	26/26	2	91		1.15	–2.32 to 4.62	0.515	0.532
	T4	48 months	33/27	2	81		0.52	–2.95 to 3.99	0.770	0.707
Maxillary arch width 2	T1	0 months	12/8	1	0	MD	–0.50	–3.73 to 2.73	0.761	–
[C(5)-(5)′] (mm) (Fig. 5C)	T2	6 months	12/8	1	0		0.09	–4.08 to 4.26	0.966	NT
	T3	18/19.5 months	12/8	1	0		3.03	–0.31 to 6.37	0.075	NT
	T4	48 months	35/30	2	53		1.43	–0.55 to 3.40	0.156	NT

Table 7. **Continued**

Variable	Time point	Follow-up	Sample size (*n*) PSIO+/PSIO–	No of studies	Heterogeneity (I^2), %	Metric (RE)	Point estimate	95% Confidence interval	*p*-Value[#]	Between time points *p*-Value (compared to T1)
Maxillary arch width 3 [P2(5-(5)′] (mm) (Fig. 5D)	T1	48 months	35/30	2	79	MD	1.24	−1.89 to 4.37	0.437	–
Maxillary arch form 1	T1	0 months	35/30	2	46	MD	2.64	0.26 to 5.02	**0.029***	–
[(M-T-C(5)] (°) (Fig. 5E)	T2	6 months	33/29	2	0		2.43	−0.52 to 5.37	0.106	0.945
	T3	18/19.5 months	26/26	2	0		1.78	−1.52 to 5.08	0.291	0.713
	T4	48 months	21/19	1	0		2.82	0.15 to 5.49	**0.038***	0.849
Maxillary arch form 2	T1	0 months	35/30	2	0	MD	0.09	−5.55 to 5.73	0.975	–
[(M-T′-C(5)′] (°) (Fig. 5F)	T2	6 months	33/29	2	92		−0.80	−6.58 to 4.99	0.787	0.840
	T3	18/19.5 months	26/26	2	24		−0.05	−5.78 to 5.68	0.986	0.986
	T4	48 months	21/19	1	0		1.94	−5.75 to 9.63	0.621	0.402
Maxillary arch form 3	T1	0 months	12/8	1	0	MD	−6.79	−24.11 to 10.53	0.442	–
[P′-C(5)-T] (°) (Fig. 5G)	T2	6 months	12/8	1	0		7.10	−9.50 to 23.70	0.402	NT
	T3	18/19.5 months	12/8	1	0		−4.34	−20.82 to 12.14	0.606	NT
	T4	48 months	22/19	1	0		−2.29	−25.19 to 20.61	0.845	NT

PSIO+, patients who received pre-surgical infant orthopedic treatment; PSIO–, patients who did not receive pre-surgical infant orthopedic treatment; MD, mean difference; SMD, standardized mean difference; RE, random-effects model; NT, not tested.

[#]Regarding the test of null for the MD/SMD.

*Significant at $p < 0.05$.

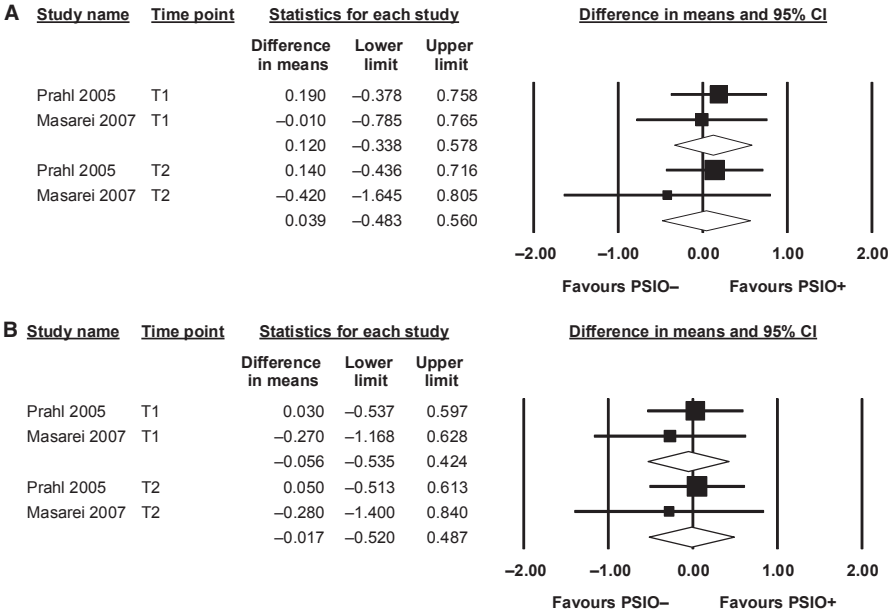

Fig. 2. Forest plots for the mean differences in weight (A) and height (B) between PSIO+ and PSIO– CLP patients. T1, time point: 3–4 months; T2, time point: 12 months; CLP, cleft lip and palate; PSIO, pre-surgical infant orthopedics.

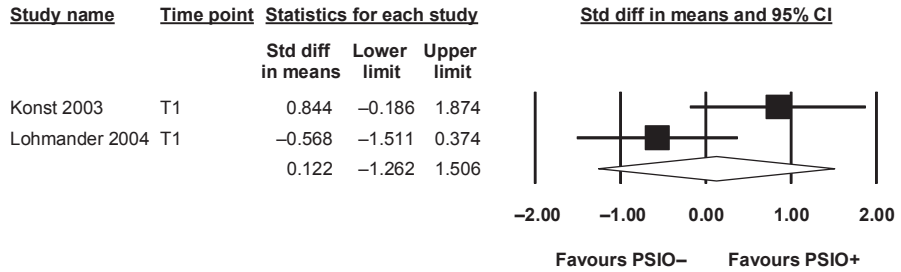

Fig. 3. Forest plot for the mean differences in speech development between PSIO+ and PSIO– CLP patients (time point of evaluation: 1.5–2 years). CLP, cleft lip and palate; PSIO, pre-surgical infant orthopedics.

data. More specifically, apart from the post-surgical T1 time point, this angle was increased in PSIO+ patients by 2.82° (95% CI = 0.15 to 5.49°; $p = 0.038$) at 48 months (T4) of follow-up (Table 7). Furthermore, no significant MDs were found for the angles M-T′-C(5) or P′-C(5)-T between PSIO+ and PSIO– patients. Finally, no significant heterogeneity was present between the subgroups of time points for any of the three angles, indicating that the long-term effect of PSIO on the maxillary arch form of CLP patients did not differ from the short-term effect. The comparison regarding the angle P′-C(5)-T included data only from one source study, and thus, no meta-analytic comparison between the time points was possible to be made (Fig. 5G).

Discussion

The effectiveness of PSIO treatment remains a subject of controversy in the medical literature. Although PSIO has not been fully established by evidence-based studies, it has become part of the standard care of CLP patients as a preliminary technique included in the treatment protocols of many centers around the world [i.e., the Americleft project (67), the Eurocleft project (68), the Cleft Palate Centres of Nijmegen, Amsterdam, and Rotterdam (55), the North Thames Regional Cleft Centre (NTRCC) (54), and the Cleft Centre of Sahlgrenska University Hospital, Göteborg (61)].

Conflicting conclusions from the published studies combined with the lack of systematic or meta-analytic investigations led to the decision of

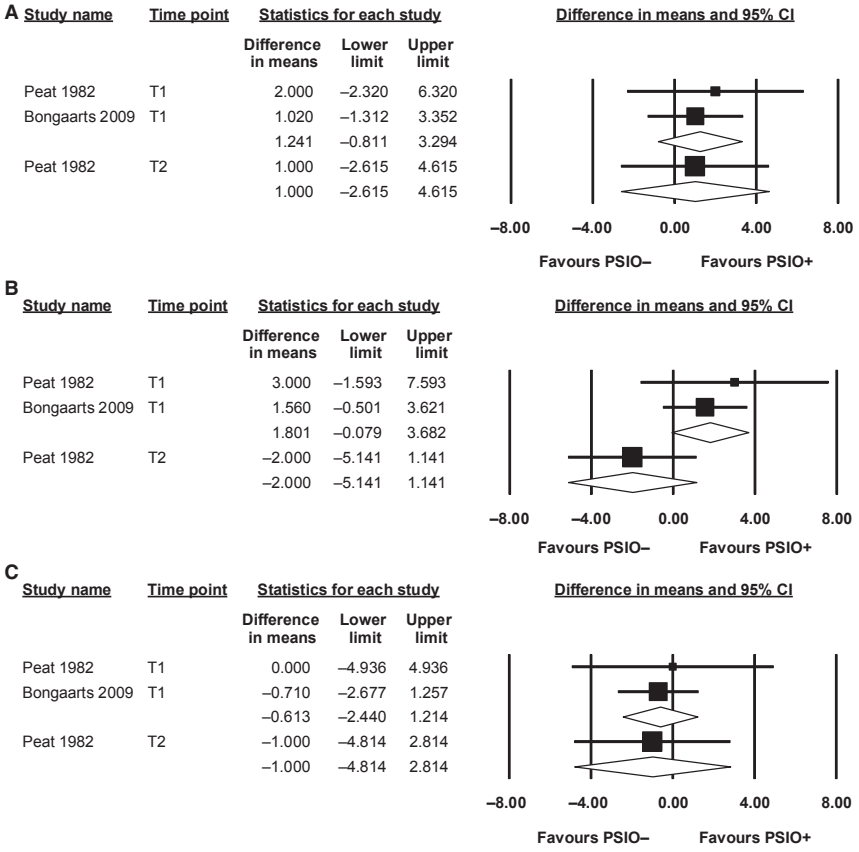

Fig. 4. Forest plot for the mean differences in the SNA angle (A), SNB angle (B) and SN-MP angle (C) between PSIO+ and PSIO– CLP patients. T1, time point: 4–5 years; T2, time point: 9.2 years; CLP, cleft lip and palate; PSIO, pre-surgical infant orthopedics.

conducting this systematic review in order to assess in an evidence-based manner the effectiveness of PSIO treatment in CLP patients. A similar systematic review (69) evaluating PSIO treatment has been published recently; however, it did not include any data synthesis by meta-analytic procedures. In the present study, a wide range of outcomes possibly affected by PSIO were examined with a comprehensive search procedure. Our search strategy covered published material up to 2010, using exhaustive electronic, manual, and gray literature searching, with no exclusion criteria based on language or publication date. Screening and selection were performed in duplicate, and data were finally pooled from 24 controlled trials, most of which were conducted during the last 15 years.

Studies comparing patients from different centers or studies with control groups consisting of healthy patients were excluded. Controlled CTs in which the study design was not clearly defined (as prospective or retrospective), and a decision could not be made, were also eliminated as retrospective CTs. Only randomized and prospective controlled CTs were included, in an attempt to reduce the risk of bias (29).

Every effort to diminish bias was made. Sampling bias was minimized, because the patients in the included trials originated from university departments (61–65) or academic hospitals and CP centers (43–60, 66). Bias concerning eligibility and quality of the original studies was tackled by having two authors independently assessed the articles, and any disagreement was resolved by consulting the first author until a final consensus was achieved. Various outcomes were included in the meta-analysis in an attempt to quantify trends of existing data. Furthermore, the RE model was used for data analysis, which in the presence of heterogeneity tends to be more conservative and produce wider CIs (38).

In general, according to the results of the current investigation, PSIO treatment seems to have no significant clinical effect in CLP patients. However,

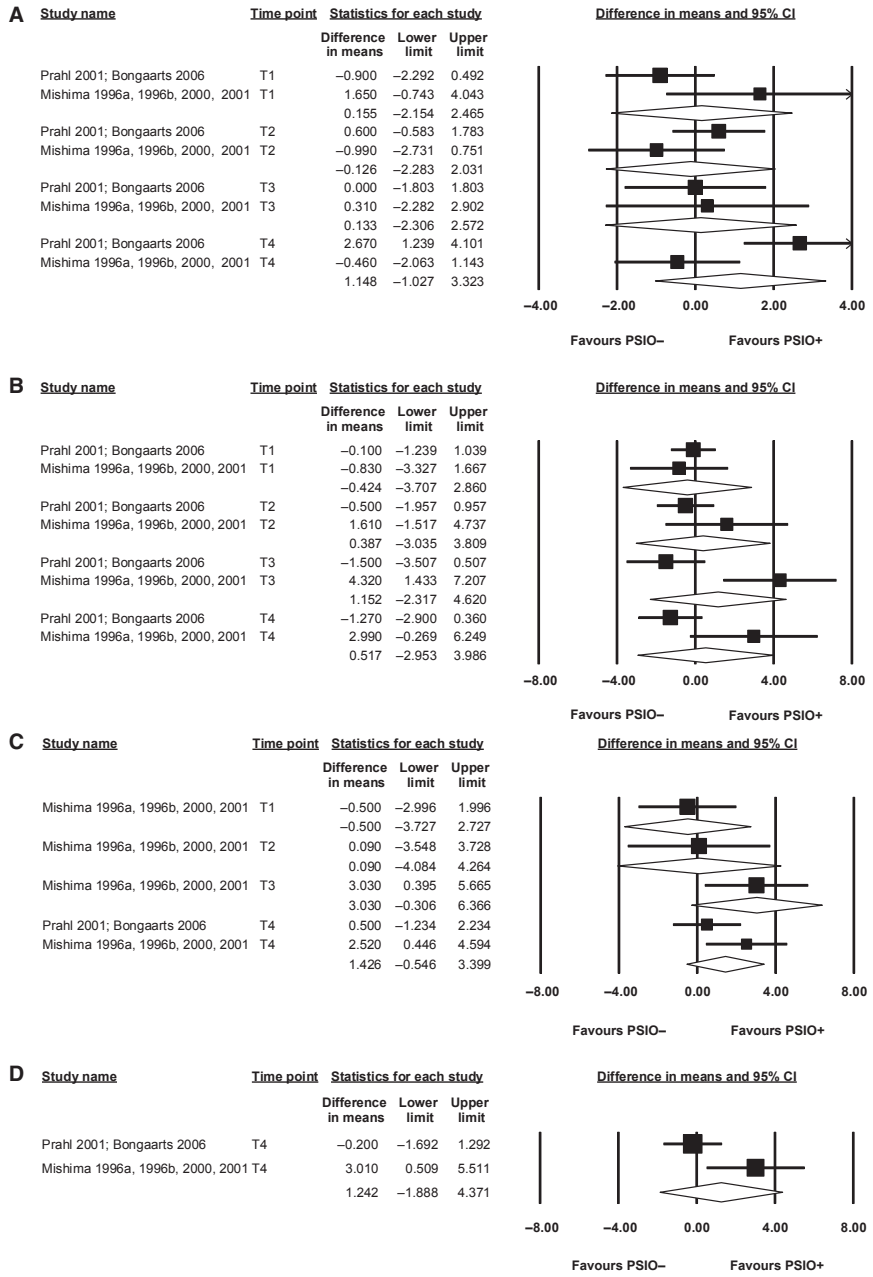

Fig. 5. Forest plots for the mean differences in the maxillary arch depth (A), maxillary arch width I (variable TT′) (B), maxillary arch width II [variable C(5)-(5)′] (C), maxillary arch width III [variable P2(5)-(5)′] (D), maxillary arch form I [variable M-T-C(5)] (E), maxillary arch form II [variable M-T′-C(5)′] (F), and maxillary arch form III [P′-C(5)-T] (G) between PSIO+ and PSIO− CLP patients. T1, time point: 1–2 weeks; T2, time point: 6 months; T3, time point: 18–19.5 months; T4, time point: 48 months; CLP, cleft lip and palate; PSIO, pre-surgical infant orthopedics.

certain limitations should be taken into consideration. All comparisons undertaken included a maximum of two compatible studies, thus minimizing the power of the evidence and precluding analyses of sensitivity or publication bias. Although moderate heterogeneity was present, except for some extreme cases, no actions could be made to eliminate it. Therefore, the summaries provided should by no means be regarded as robust, but only as an insight into existing knowledge, which could serve as a starting point for future studies with more rigorous designs.

According to the results of the undertaken meta-analysis, PSIO treatment seems to have little effect on the feeding ability and subsequent growth (investigated through weight and height),

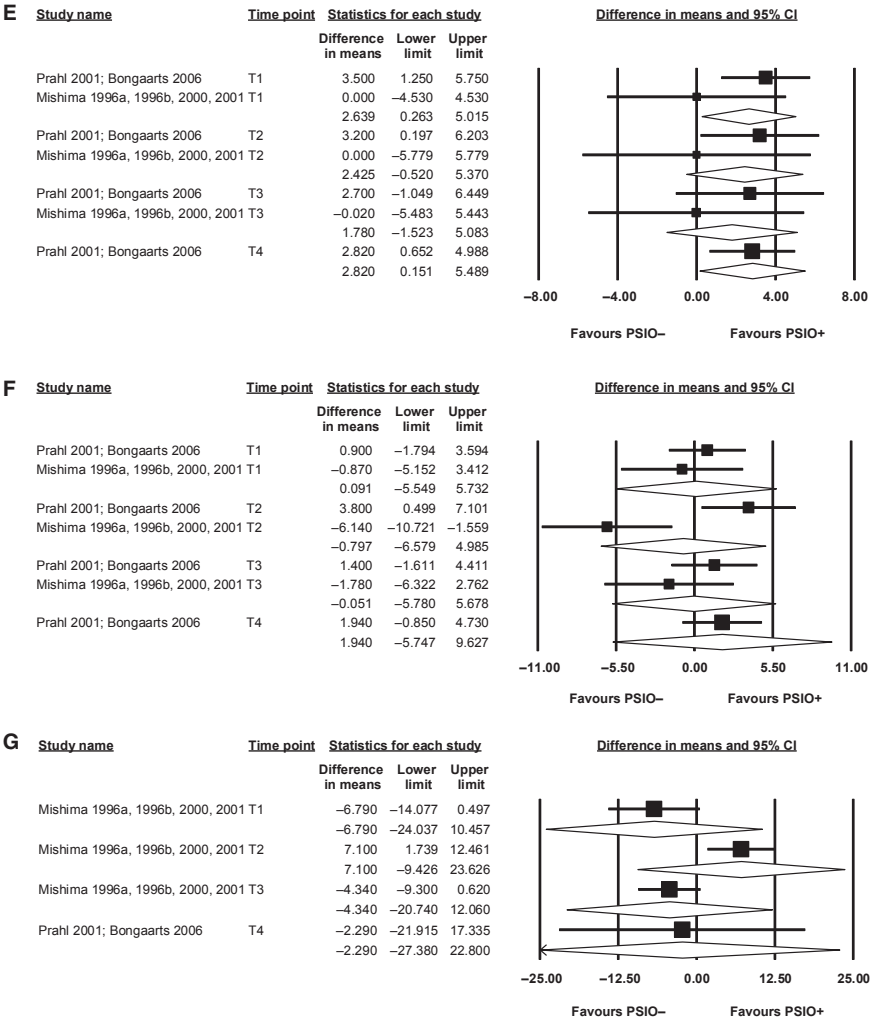

Fig. 5. Continued.

as well as on speech (investigated through the number of consonants) of patients with CLP (Fig. 2) during the first 2 years of life. As demonstrated by Konst et al. (47–52) in detailed investigations, PSIO treatment had positive but probably only temporary effects on speech and language development of CLP patients (Fig. 3). Treated infants had a significantly more normal phonological development path, improved production of alveolar contoids and oral plosives, superior intelligibility, and longer utterances in their speech, but these treatment effects faded away as the infants grew up, at the age of 6 years (47–52).

There seems to be no clinically positive effect of PSIO treatment on facial growth of CLP patients until the age of 6 years (45). This finding is in agreement with the study of Peat (66), who examined BCLP patients and assessed their craniofacial outcomes by the SNA, SNB, and SN-MP angles up to 9 years of age. The same author found also a tendency for less incisor crossbite in the PSIO+ group, but this should be interpreted with caution, because of the small sample size of this study (66). In our investigation, only limited data from the included studies could be used for quantitative synthesis, pointing out a slight, non-significant trend toward an increased SNB angle by 1.8° in PSIO+ patients at the age of 4–5 years (Fig. 4), which, however, became definitively non-significant at the 9.2 years of follow-up. Furthermore, according to the results of the qualitative review, it seems that PSIO had no considerable lasting effect on facial esthetics when assessed by full-face and nasolabial photographs (46, 58).

According to the qualitative assessment of the results of the Dutchcleft studies, it can be concluded that neither occlusion (examined up to 6 years) (43) nor the contact or collapse status of the maxillary segments of CLP patients was influenced following PSIO treatment (44, 56). Further, the results of the meta-analysis indicate that PSIO has no significant effect on maxillary arch depth and width. This is in agreement with the findings of a previous systematic review (69), in which no differences between PSIO+ and PSIO− infants were found with regard to these parameters. The only positive effect of PSIO found in the current investigation was on the maxillary arch form of CLP patients, as measured by one of three variables [M-T-C(5)] included in the analysis (Fig. 5). Nevertheless, the latter result should be considered however, with some caution, because this positive effect was not in present at all time points. It is claimed that a wider arch form decreases the size of the buccal corridor spaces and therefore improves the smile value and consequently facial esthetics (70, 71). Thus, if this finding would be confirmed by future studies, it could probably mean that PSIO treatment may result in a better facial appearance of CLP patients.

Apart from the evaluation of clinical outcomes, cost-effectiveness analyses were also included in the original studies in order to correlate the cost of PSIO treatment with its effects. Severens et al. (60) in a short-term cost evaluation suggested that the cost-effectiveness of PSIO+ over PSIO− treatment did not seem to be acceptable with regard to the operating time needed for surgical lip closure. Despite the significant cost of PSIO treatment, the duration of lip surgery was almost the same as in PSIO− patients. However, other variables such as easiness of surgery, appearance or function of the orbicularis oris after lip closure were not included in their analysis. In contrast, Konst et al. (53) in a long-term cost analysis showed that, in terms of speech development, the cost-effectiveness in PSIO+ over PSIO− patients seemed to be acceptable, because treated infants had a small but significant improvement in speech development at the age of 2.5 years (1041 euro for 1.34 point of speech improvement).

According to the results of the qualitative evaluation, motherhood satisfaction, which was investigated through questionnaires, was not affected during the first year of patients' life (59).

The results of this study are valid for the passive type of appliance used mainly on UCLP patients. It was not possible to draw conclusions for active plates or appliances with extensions for nasoalveolar molding. Future RCTs investigating these types of appliances as well as BCLP patients would be useful. Although some studies indicate a beneficial use of pre-surgical nasoalveolar molding (PNAM) treatment (12, 72, 73), particularly for the improvement of nasal symmetry, these results remain to be supported.

Despite the concurrence of reports on surgery, and although it is already recognized by Winters and Hurwitz (74), no RCT was found investigating the possible benefits of PSIO to cleft surgery. Such results are expected from a trial that is currently taking place in the North Thames Regional Cleft Centre (NTRCC) in the UK (54). So far, it appears that the Dutchcleft studies (43–53, 55–60) are the best-designed RCTs currently available. The NTRCC trial (54) utilizes a similar rigorous methodology, yet only the first part of the results concerning the effects of PSIO treatment on feeding has been published up to now.

Conclusions

Short- and long-term effectiveness of PSIO treatment was examined in patients with complete UCLP, mainly with respect to the passive type of appliance. According to the results of this meta-analysis, only 3 of 13 variables were found to present some significant differences. However, this positive effect was not present at all time points. Thus, existing evidence cannot support the short- or long-term effectiveness of PSIO treatment in CLP patients.

In the future, well-designed RCTs with long-term follow-up should be undertaken in order to provide additional evidence to confirm or reject PSIO effectiveness.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Articles with full texts not available.

Table S2. Articles excluded on basis of full-text from this study and reason for exclusion.

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